REMARKS

In the instant Office Action, claims 1-9 are listed as pending, claims 6 and 10-12 are withdrawn from consideration by the Examiner, claim 7 is objected to, and claims 1-5, 8 and 9 are rejected based on the Examiner's extended search to include N-Me-Ala^8 and N-Me-Gly^8 derivatives of hGLP-1(7-36)-NH_2, which newly species read on claims 1-5, 8 and 9.[1]

1. In the instant Office Action, the Examiner has acknowledged Applicants' Response filed on March 14, 2006 (the "March 14 Response"), wherein Applicants amended the *specification* to provide a definition of the abbreviation "Hppa" and pointed out that a derivative having hydroxyphenylpropionic acid is disclosed at page 30 of Sequence Listing. Consequently, the Examiner withdrew the rejections of record and introduced a new ground of rejection. Citing MPEP §706.07(a), the Examiner made the instant Office Action final. Applicants respectfully traverse the finality of the instant Office Action.

MPEP §706.07(a) states, in relevant part:

> Under present practice, second or any subsequent actions on the merits shall be final, except where the examiner introduces a new ground of rejection that is neither necessitated by applicant's ***amendment of the claims*** ...
>
> A second or any subsequent action on the merits in any application ... should ***not*** be made final if it includes a rejection, on prior art not of record, of any ***claim*** amended to include limitations which should reasonably have been expected to be claimed. ... For example, one would reasonably expect that a rejection under 35 U.S.C. 112 for the reason of incompleteness would be replied by an amendment supplying the omitted element. (emphasis added)

[1] In the instant Office Action, at page 2, the Examiner states that "Claims reading the selected species are 1-5, 8." Applicants believe that it was an obvious typographical error to not include claim 9 as reading on the selected species, based on the fact that the Examiner goes to reject claims 1-5, 8 and 9 under 35 U.S.C. §103(a) based on the selected species.

In the March 14 Response, on page 13, it is expressly set forth that "Applicants have ***not*** amended, canceled or withdrawn any pending ***claims***." (emphasis added) Instead, in response to a rejection under 35 U.S.C. §112, second paragraph, Applicants merely amended the ***description*** to specifically include "Hppa" in the list of abbreviations for synthetic amino acids used in the claimed substituted analogues as found on page 9 of the international publication of the parent PCT application, *i.e.*, WO 00/34332. (*See* page 14 of the March 14 Response") Since it is clear that the Examiner's new ground of rejection in the instant Office Action was not necessitated by Applicants' amendment of the ***claims***, Applicants respectfully submit that the Examiner misapplied MPEP §706.07(a) and request that the Examiner withdraw the finality of the instant Office Action.

Assuming, *arguendo*, Applicants amended the pending claims – which they clearly did not – MPEP §706.07(a) provides that the Examiner should *not* have made the instant rejection *final* of any claim amended to include limitations which should reasonably have been expected to be claimed. In this case, even if Applicants had amended the pending claims to overcome the rejection under 35 U.S.C. §112, second paragraph, the Examiner should have reasonably expected such rejection would be replied by an amendment supplying the omitted element. In this regard, MPEP §706.07 provides, in relevant part:

> Before a final rejection is in order a clear issue should be developed between the examiner and applicant. ... While the rules no longer give an applicant the right to "amend as often as the examiner presents new references or reasons for rejection," present practice does not sanction hasty and ill-considered final rejections. The applicant who is seeking to define his or her invention in claims that will give him or her the patent protection to which he or she is justly entitled should receive the cooperation of the examiner to that end, and not be prematurely cut off in the prosecution of his or her application.

In this case, however, it is apparent that the Examiner made the instant Office Action *final* in response to *any* amendment to the application, for *any* reason.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the finality of the instant Office Action, pursuant to MPEP §706.07(d), which provision sanctions withdrawal of the finality of a *premature* final rejection.

2. In the event that the Examiner will not withdraw the finality of the instant Office Action, Applicants file concurrently with this reply a "conditional" request for continued prosecution (RCE) under 37 C.F.R. §1.114. **Please note that the present RCE is "conditional" upon the Examiner's maintenance of the finality of the instant Office Action.**[2] That is, in the event the Examiner withdraws the finality of the instant Office Action, Applicants respectfully request that the Examiner treat the present RCE as being improper (*i.e.*, continued examination under 37 C.F.R. §1.114 does not apply to an application unless prosecution in the application is closed). On the other hand, if the Examiner maintains the finality of the instant Office Action, Applicants respectfully submit that the presently submitted RCE meets the requirements of 37 C.F.R. §1.114 since prosecution of the pending application on the merits is closed due to the finality of the instant Office Action as required under 35 U.S.C. §132. In the event that the Examiner maintains the finality of the instant Office Action, Applicants further respectfully request that the finality of the instant Office Action be withdrawn pursuant to 37 C.F.R. §1.114 and that the instant submission be entered into the record and considered.

[2] This is pursuant to MPEP §706.07(h), which provides, in relevant part:

> If a submission is accompanied by a "conditional" RCE and payment of the RCE fee under 37 CFR 1.17(e) (*i.e.*, an authorization to charge the 37 C.F.R. 1.17 (e) fee to a deposit account in the event that the submission would not otherwise be entered), the Office will treat the "conditional" RCE and payment as if an RCE and payment of the fee set forth in 37 CFR 1.17(e) had been filed.

3. The Examiner has rejected claims 1-5, 8 and 9 under 35 U.S.C. §103(a) as obvious over Buckley *et al.* (U.S.P.N. 5,545,618) and Galloway *et al.* (EP 733644 A1). In particular, at pages 3-4 of the instant Office Action, the Examiner acknowledged that the references do not teach N-Me derivatives of Ala^8-hGLP-1(7-36)-NH_2, D-Ala^8-hGLP-1(7-36)-NH_2, or Gly^8-hGLP-1(7-36)-NH_2, as instantly claimed. However, the Examiner goes on to state at pages 3-4 of the instant Office Action:

> Within the context of chemistry, unsubstituted compounds are similar to their homologue, lower alkyl (e.g., methyl) substituted compounds in the physical properties, and, because of their structural similarity, it is generally predictive that their chemical properties will be similar. Because the adjacent homologs, lower alkyl compounds -N(lower alkyl)-, would be expected to have similar physical and chemical properties as unsubstituted (-NH-) compounds, a high degree of predictability in producing a compound having the same physical and chemical properties would be expected when substituting H for lower alkyl group in a large compound. Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the preferred Ala^8 or Gly^8 GLP-1 analogs of Buckley or Galloway such that NH- group is replaced by N-Me group. Since one of ordinary skill in the art of pharmaceutical chemistry would have expected that such modification would not change the properties of a compound in a significant way, one of ordinary skill in the art would have been motivated to make such a modification so as to obtain another preferred compound with the activity disclosed in Buckley and Galloway.

However, within the context of *medicinal chemistry*, there is a huge difference between peptides containing single or multiple N-methylated amino acids and unsubstituted compounds.[3] Several natural products, *e.g.* vancomycin, cyclosporine,

[3] *See, e.g.*, F. Haviv *et al.*, "Effect of N-Methyl Substitution of the Peptide Bonds in Luteinizing Hormone-Releasing Hormone Agonists," *J. Med. Chem.*, Vol. 36, 363-369 (1993); D. P. Failie *et al.*, "Macrocyclic Peptidomimetics – Forcing Peptides into Bioactive Conformations," *Curr. Med. Chem.*, Vol. 2, 654-686 (1995); R. Schmidt *et al.*, "Structure-activity relationships of dermorphin analogues containing N-substituted amino acids in the 2-position of the peptide sequence," *Int. J. Pept. Protein Res.*, Vol. 46, 47-55 (1995); W. L. Cody *et al.*, *J. Med. Chem.*, Vol. 40, 2228-2240 (1997). Copies of these references are attached herewith for the Examiner's convenience.

actinomycine D, and lead compounds with good proteolytic stability and improved pharmacokinetic properties are based on N-methyl amino acid containing substances.[4]

In fact, in one of the references cited by the Examiner, Buckley *et al.* (U.S.P.N. 5,545,618), in support of the §103(a) rejection, the following passage is provided at Col. 3, lines 45-58:

> In another aspect, the invention is directed to peptides which show enhanced degradation resistance in plasma as compared to GLP-1(7-37) wherein this enhanced resistance to degradation is defined as set forth below. In these analogs, any of the above-mentioned truncated forms of GLP-1(7-34) to GLP-1(7-37) or their C-terminal amidated forms is modified by ...
>
> (d) substitution of an N-acylated or N-alkylated form of any naturally occurring amino acid for H at position 7.

As such, the very reference that the Examiner cites to support his obviousness rejection teaches that an N-alkylated (*e.g.*, N-methylated) form of a naturally amino acid shows *different* biological properties (*e.g.*, enhanced degradation resistance) as compared to unsubstituted (-NH-) compounds. As such, Buckley in fact *teaches against* the Examiner's position that the structural differences between an N-methylated form and an unsubstituted compound are trivial, and thus predictive of similar chemical and physical properties.

The Examiner's attention is further directed to the following passage in one of the references cited hereinabove by Applicants in support of their position that there is a huge difference between an N-methylated form and an unsubstituted (-NH-) compound in the context of medicinal chemistry:

> Substitutions of NMe-1Nal[3], NMe-1Ser[4], or NMe-1Tyr[5] in leuprolide rendered the 3-4 peptide bond in these compounds completely stable to

[4] *See, e.g.*, J. M. Ostresh *et al.*, *Proc. Natl. Acad. Sci. USA*, Vol. 91, 11138-11142 (1994); S. M. Miller *et al.*, "Comparison of the Proteolytic Susceptibilities of Homologous L-Amino Acid, D-Amino Acid, and N-Substituted Glycine Peptide and Peptoid Oligomers," *Drug Dev. Res.*, Vol. 35, 20-32 (1995). Copies of these references are attached herewith for the Examiner's convenience.

> chymotrypsin. ... N-Methylation at these positions is not only disrupting the hydrogen bond interactions, but is also sterically preventing the substrate from fitting in the enzyme's active site.[5] (Abstract)

In sum, it is widely recognized by those having ordinary skill in the area of medicinal chemistry that, to produce polypeptide and protein analogs and derivatives which have better biochemical properties, sometimes incorporation of unnatural amino acid residues into specific positions inside the polypeptides and proteins is required. Such analogs and derivatives could have improved stability, increased enzymatic stability, prolonged duration of action *in vivo*, and enhanced biological activities. One class of unnatural amino acids is the N-methyl amino acids. The N-methyl amino acids can (1) impose conformational constraint on peptide backbone, (2) block hydrogen bonding sites and (3) potentially protect the peptide bonds against enzymatic cleavage.

In further support of Applicants' position as set forth hereinabove, Applicants hereby submit Declaration of Dr. Zheng Xin Dong, under 37 C.F.R. §1.132.

Lastly, Applicants submit that the Examiner has failed to establish an element necessary to make out a *prima facie* case of obviousness, that of showing some suggestion or motivation in the prior art to combine prior art elements in order to arrive at the subject matter claimed in the instant application. The Examiner has cited no prior art which would support such a suggestion in this case, *i.e.*, that one of ordinary skill in the field of medicinal chemistry *should* come up with N-Me derivatives of Ala^8-hGLP-1(7-36)-NH_2, D-Ala^8-hGLP-1(7-36)-NH_2, or Gly^8-hGLP-1(7-36)-NH_2, as instantly claimed. As to motivation, the Examiner has merely opined that, as a *general* proposition, within the context of chemistry, unsubstituted compounds are similar to their homologue, lower alkyl

[5] F. Haviv *et al.*, "Effect of N-Methyl Substitution of the Peptide Bonds in Luteinizing Hormone-Releasing Hormone Agonists," *J. Med. Chem.*, Vol. 36, 363-369 (1993)

substituted compounds in the physical properties, and, because of their structural similarity, it is *generally* predictive that their chemical properties will be similar.

Assuming, *arguendo*, that the Examiner has made out a *prima facie* case of obviousness, the rejection fails for the reasons as discussed hereinabove. That is, it is well-recognized by those having ordinary skill in the area of medicinal chemistry that the structural difference between an N-methylated form of GLP-1 and an unmodified compound is significant, and therefore, their widely varying biochemical properties.

Furthermore, a *prima facie* case of obviousness based on structural similarity is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties. MPEP §2145 (citing *In Re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)) In this regard, Applicants discussed hereinabove numerous scientific papers and Dr. Dong's Declaration under 37 C.F.R. §1.132 showing that the N-methyl amino acids can (1) impose conformational constraint on peptide backbone, (2) block hydrogen bonding sites and (3) potentially protect the peptide bonds against enzymatic cleavage.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a).

4. Applicants are grateful for the conditional allowance of claim 7. Applicants, however, have not amended claim 7 in independent form including all of the limitations of the base claim and any intervening claims, as directed by the Examiner, in anticipation that the Examiner will withdraw the rejection of claim 1 in view of Applicants' argument hereinabove. Applicants respectfully request a subsequent opportunity to amend claim 7, as suggested by the Examiner, in response to a later Office Action or if the rejection of claim 1 is maintained.

5. Applicants respectfully request, in the event that the Examiner finds that any of claims 1-7, 8 and 9 are patentable, the rejoinder of withdrawn claims 10-12 since such claims require the use of patentable subject matter. As noted in MPEP §821.04:

> [I]f Applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims which depend from or otherwise include all the limitations of the allowable product claim will be rejoined.

Applicants submit that claims 10-11 currently incorporate the limitation of claim 1 by the language "a compound according to claim 1." In a similar manner, claim 12 currently incorporates the limitations of claim 1 by the language "according to claim 11" wherein claim 11 incorporates the compound according to claim 1. Therefore, Group II and Group III claims would be appropriate for rejoinder upon allowance of Group I product claims 1-9.

CONCLUSION

Reconsideration of the instant Office Action and allowance of all pending claims are respectfully requested. Prompt and favorable action is solicited. Should Examiner Borin deem that any further action by the Applicants would put this application in order for acceptance, he is requested to contact the Applicants' undersigned representative.

Respectfully submitted,

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